

- ▣ Benefit of so many drugs ...

  - ❖ QOL

  - ❖ Mortality

- ▣ Novel biologicals add an extra risk of opportunistic infections (TB, PJ, NTM, *Nocardia*)

- ▣ Background of cigarette smoking needs be taken into account

# Issues with DIRD

## ❑ Level of evidence generally low

- ❑ Pulmonary infiltrates
- ❑ BAL (15.2%)
- ❑ Search for an infection ...
- ❑ HD corticosteroids
- ❑ Short-term follow up

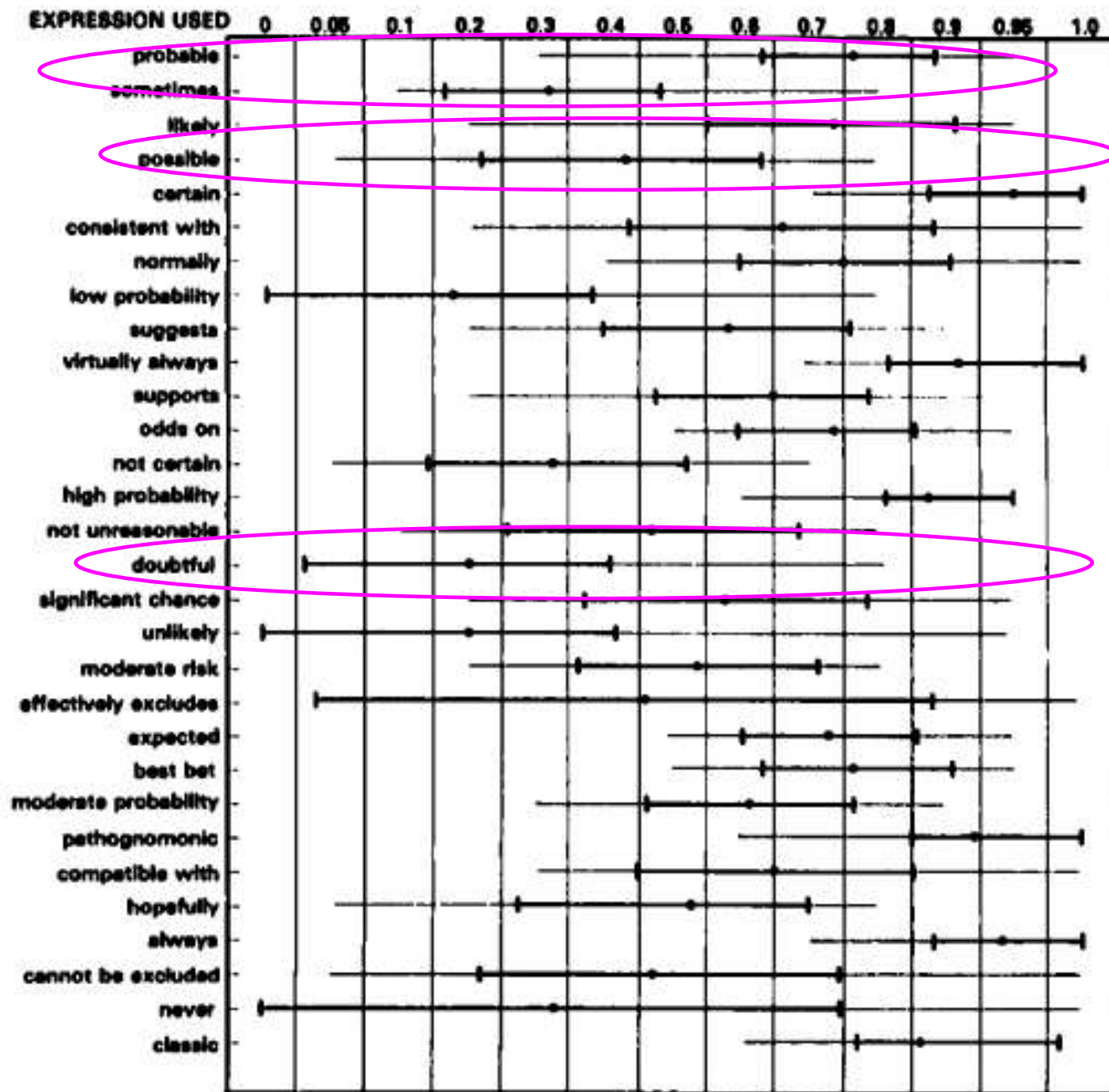
## ❑ Rechallenge: 2.7%

## ❑ Rechallenge with relapse: 1.4%

**Table I. ADR probability scale**

To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score.

	Yes	No	Do not know	Score
1. Are there previous <i>conclusive</i> reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a <i>specific</i> antagonist was administered?	+1	0	0	
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in <i>any</i> previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
				Total score



# Where are the patients ?

- ▣ Pulmonary
- ▣ Intensive / emergency care
- ▣ Internal medicine
- ▣ Rhumatology
- ▣ Cardiology
- ▣ Onco-hematology
- ▣ Oncology
- ▣ Transplantation
- ▣ Anesthesiology
- ▣ 'Transfusion medicine
- ▣ Dental care
- ▣ Veterinarians

# Who is at risk ?

## □ Patient-related

- ▣ Renal failure (platinum)
- ▣ Low albumin
- ▣ Smoking (short-term, longterm) (rarely protective)
- ▣ A slow acetylator phenotype (DPH)
- ▣ HLA-A3 B35 Dw1 BfF C4A3,2 (Gold)
- ▣ Ethnicity
- ▣ Low DLCO
- ▣ Preexisting ILD/IPF/Rheumatoid lung
- ▣ PVOD
- ▣ NOT LHF
- ▣ Deveopment of ANA/MPO-ANCA while on the drug

# Who is at risk?

## ▣ Drug-related

- ▣ Dosage
- ▣ Out of range coagulation studies
- ▣ IV vs. oral or s/C
- ▣ Rapid infusion
- ▣ Longterm treatment (NF, CPM)
- ▣ Storage of compound or metabolite in lung (Amio)

## ■ Potentiating conditions

- Radiation therapy
- Multiagent regimens
- Unnecessarily high oxygen therapy
- Drug-drug interactions
- Second hit (surgery, sepsis)



## □ Disease-related

- High white blood cell counts
- APML

# Diagnosis: Practical considerations

## ■ Exposure to the drug or drugs

- ▣ Route of administration
- ▣ History of prior exposure to drugs (adverse consequences?)



- ▣ History taking for each drug (Drug monitoring specialists)
- ▣ Concomittant medications
- ▣ History of transfusion
- ▣ Exposure to oxygen
- ▣ History of any procedure (recent, remote)

# Signs & symptoms develop AFTER exposure

## ▣ Within hours

- ❖ Asthma, anaphylaxis, embolism, pulmonary edema, DAD, ARDS

## ▣ Days

- ❖ Pulmonary edema, DAH, ARDS

## ▣ Weeks-Months

- ❖ ILD, eosinophilic pneumonia, BOOP

## ▣ Years

- ❖ Amio
- ❖ Fibrosis

## ▣ Delayed after withdrawal

- ❖ Fibrosis, PPFE

# Drug singularity

## □ Ideal situation

- ▣ Young person, eosinophilie pneumonia

## □ Otherwise

- ▣ Complete list of drugs
- ▣ Draw a drug-pattern-frequency contingency table
- ▣ Withdrawal
  - ❖ Starting with the most likely culprit
  - ❖ All drugs if ARF
- ▣ Rechallenge
  - ❖ Starting with the least likely drug and up

# Baseline pulmonary stautus

- **Imaging (radiograph, CT)**
- **PFT**
- **DLCO**

# Responsibility of the underlying disease

- ▣ **RA**: NSIP, BOOP, DAD, fibrosis, bronchiolitis, nodules, PHTn, pleuritis/effusion
- ▣ **Lupus**: DAH, NSIP, PHTn, embolism, pleuritis
- ▣ **IMM**: BOOP, NSIP
- ▣ **Scleroderma**: fibrosis, PHTn
- ▣ **Polyangitis**: vasculitis, PIE, BOOP
- ▣ **IBD**: NSIP, BOOP, PIE
- ▣ **LHF**: pulmonary edema, DAH
- ▣ **SOT**: infection

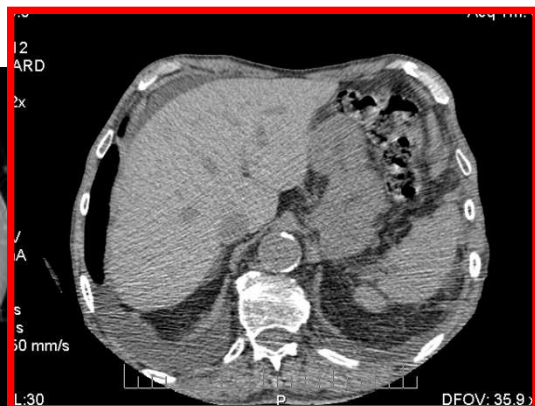
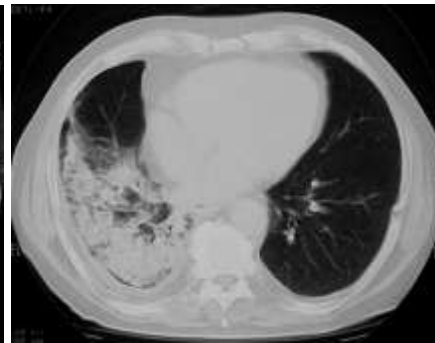
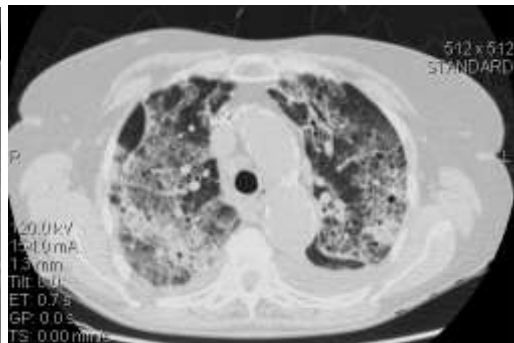
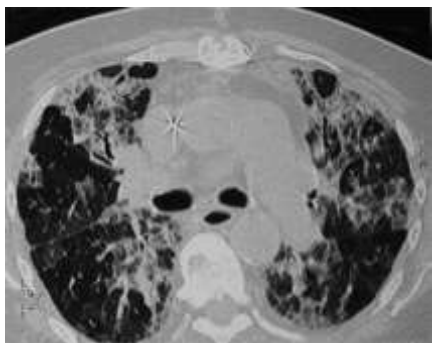
# A few specific patterns

## ❑ Amiodarone pulmonary toxicity (APT)

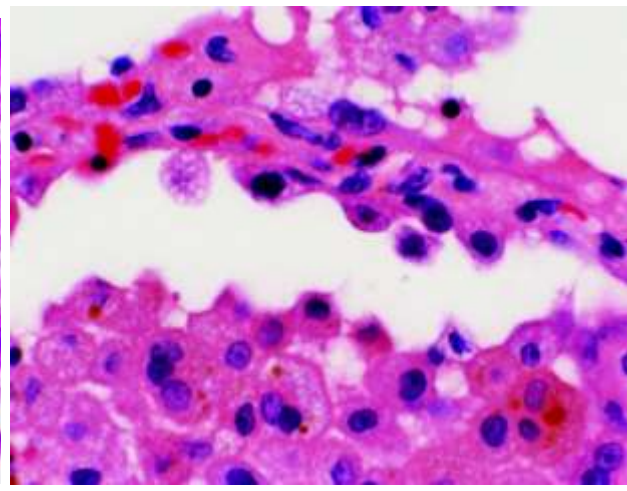
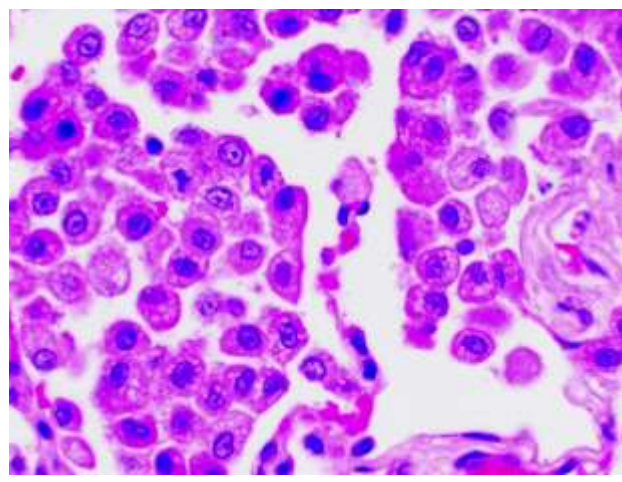
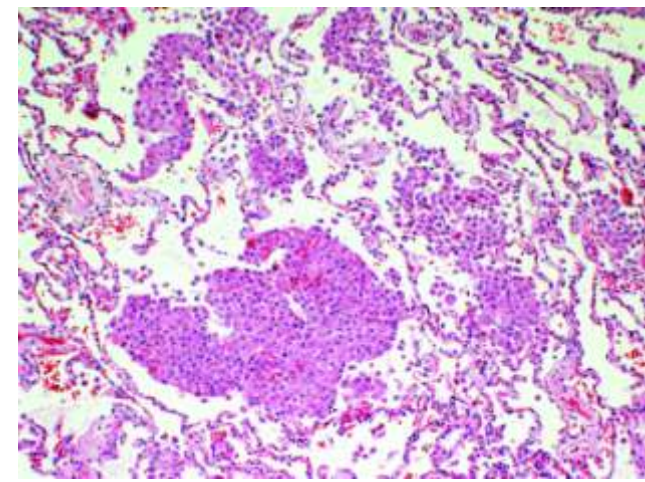
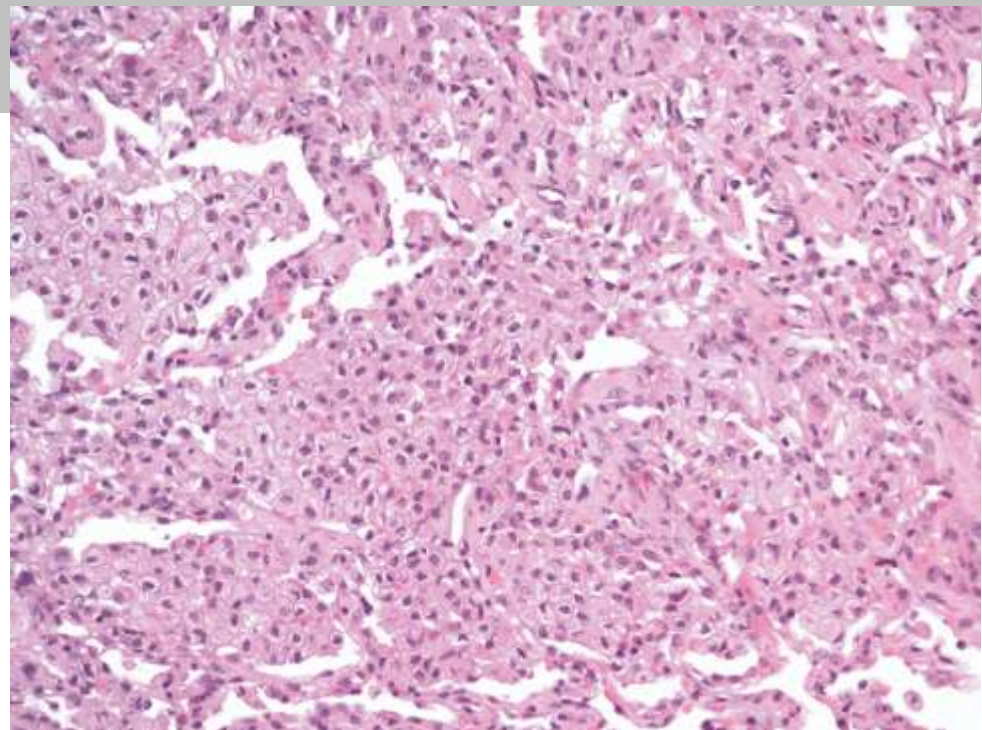
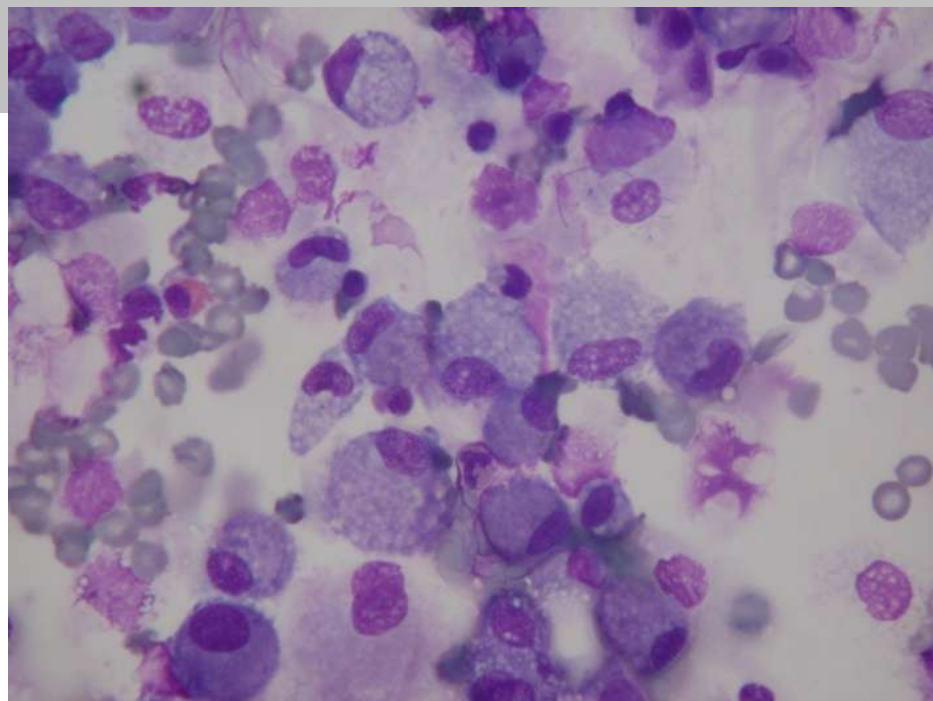
- ❑ Typical age >60 / 6-12 mo into treatment (150-180 g)
- ❑ Insidious onset (weeks-months)
- ❑ Dyspnea, cough, moderate fever, pleuritic chest pain
- ❑ Multiple possible presentations





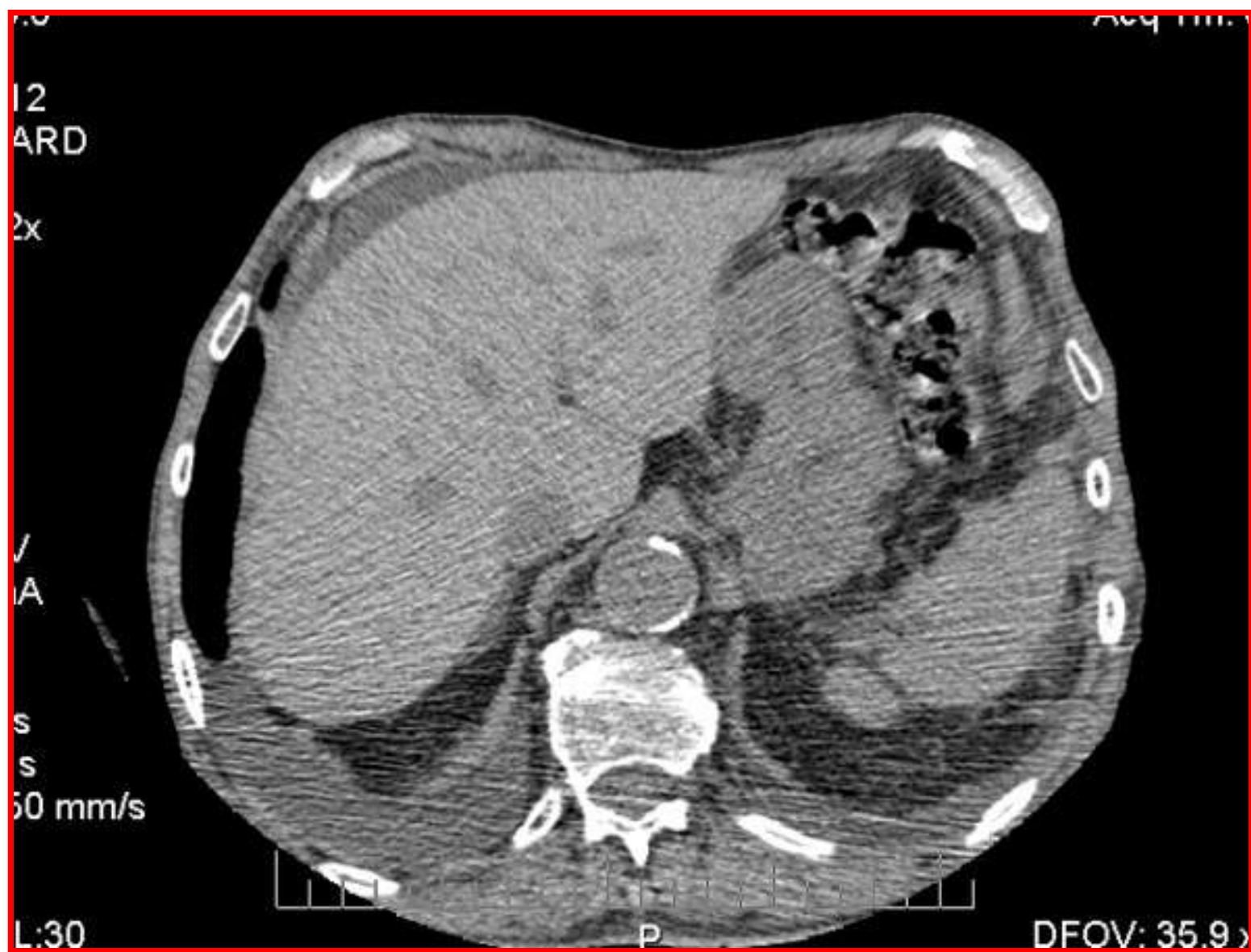






## ▣ **Amiodrone lung: diagnosis**

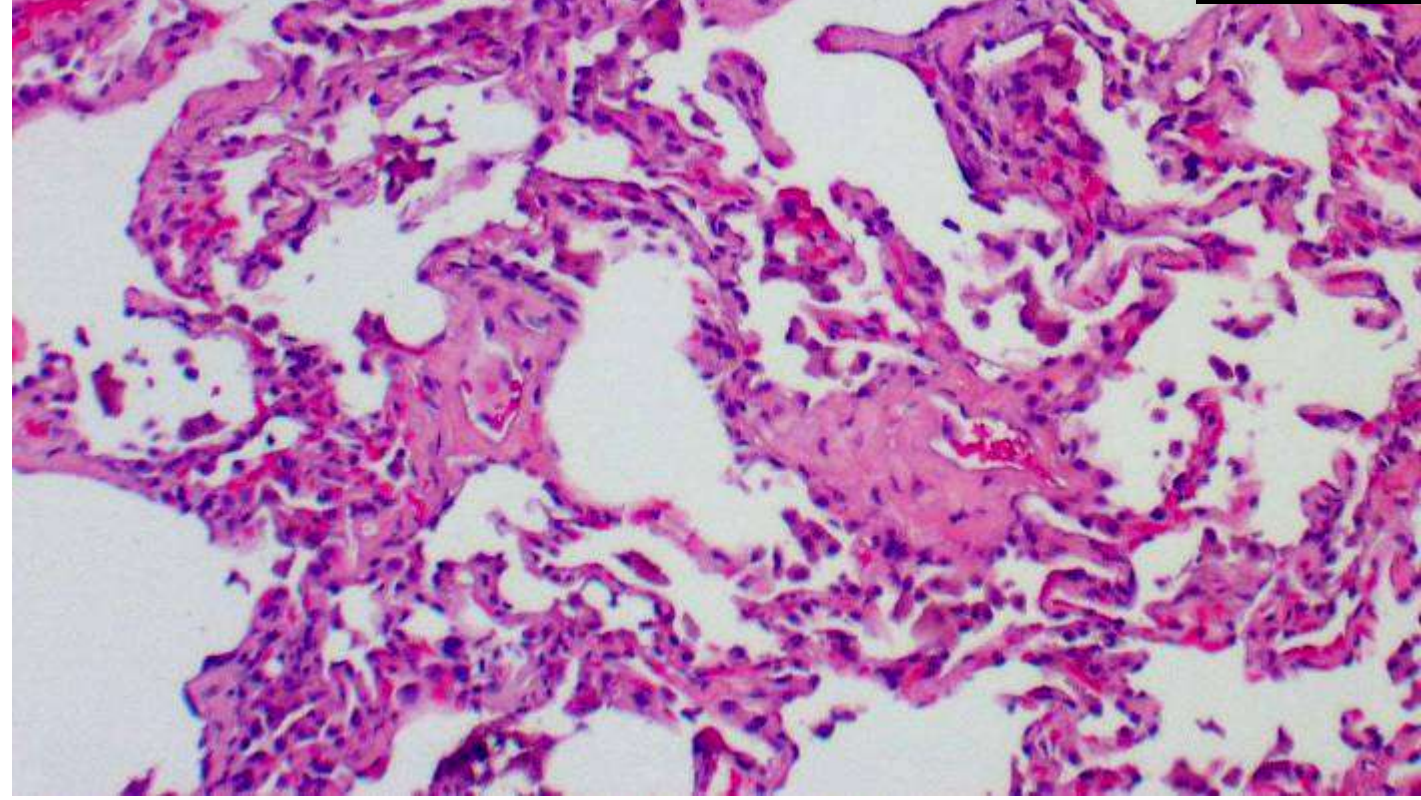
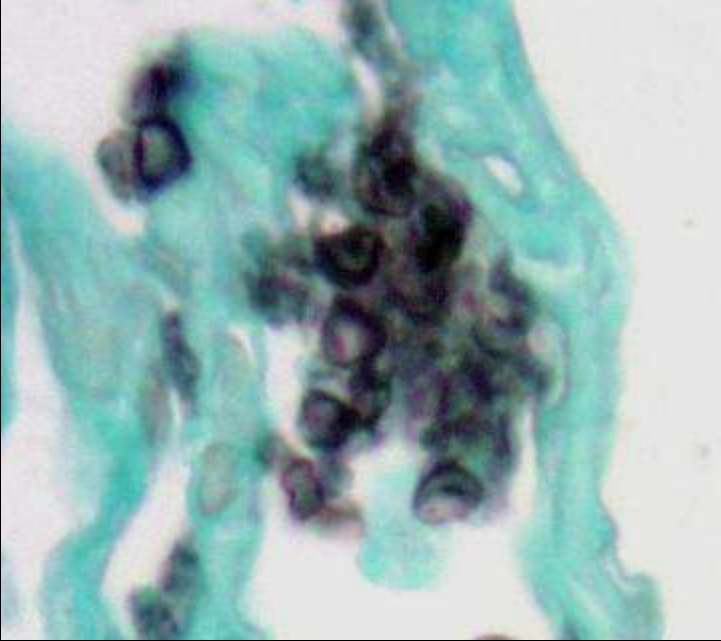
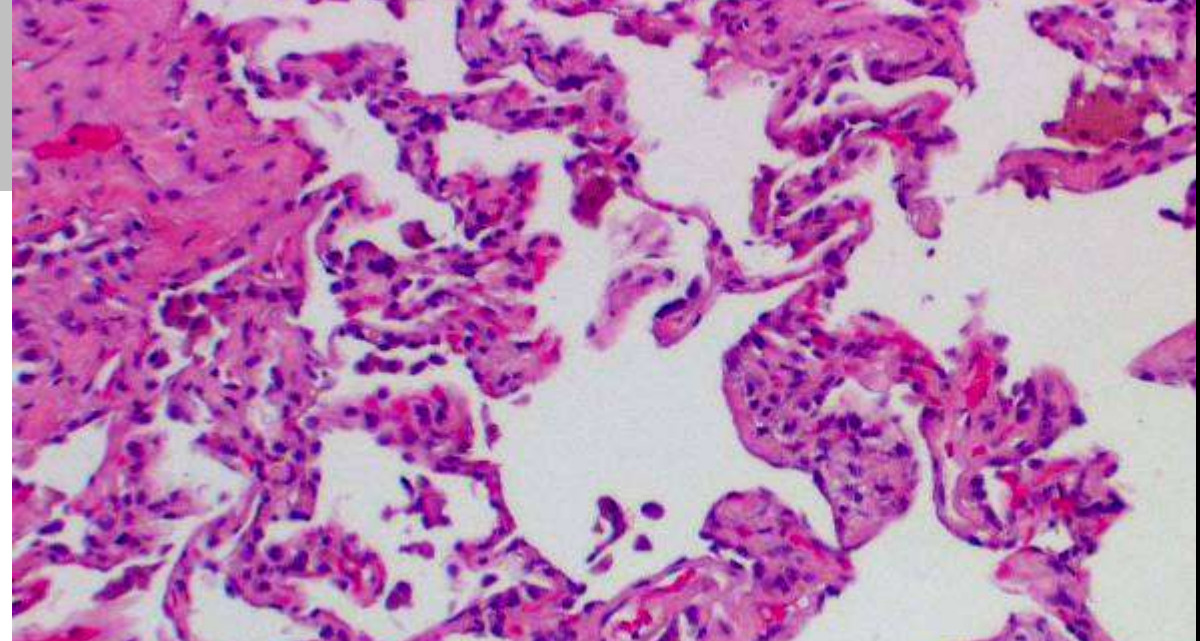
- ❖ Imaging
- ❖ Normal heart US
- ❖ Unchanged NT-pro-BNP
- ❖ *Cath Pw*
- ❖ Diuresis
- ❖ BAL
  - ▣ Amiodarone effect
  - ▣ +/- Inflammation
- ❖ Avoid OLB
- ❖ Empiric drug withdrawal (substitute) +/- defibrillator
- ❖ Corticosteroid therapy (longstanding)





# Lab

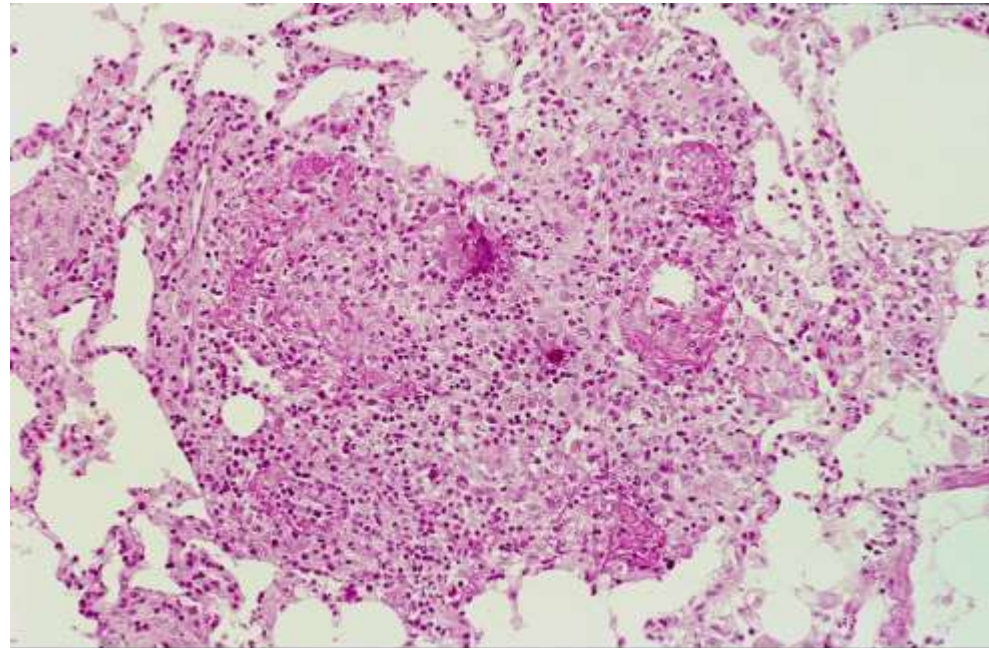
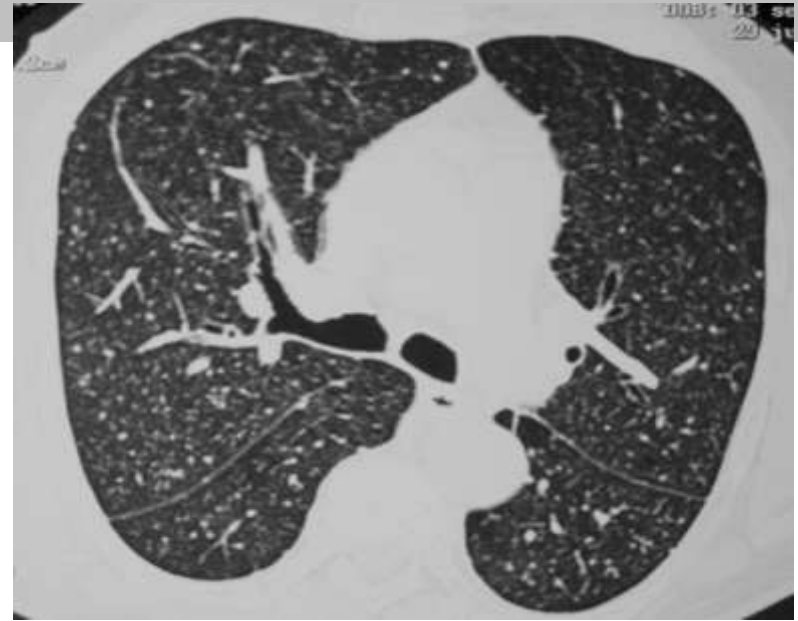
- ❑ **Blood levels: opiates, ASA, ?Amio**
- ❑ **Coagulation studies: VKA, DOA, platlets**
- ❑ ***In vitro* studies**
  - ❑ LTT: obsolete
  - ❑ KL6...
- ❑ **BAL**
  - ❑ Eosinophils
  - ❑ Lymphocytes
  - ❑ Workup for an infection
- ❑ **Pathology in selected cases**





# ILD with a granulomatous component

- ▣ Causal drugs: BCG, IVDU  
etanercept, everolimus  
interferons, methotrexate
- ▣ Rule out an infection (TB, PJ)
  - ❖ BAL
  - ❖ IGRA



**Table 1**

Frequently used additives/diluents to adulterate street drugs [22].

Quinine
Mannitol
Lactose
Glucose
Procaine
Caffeine
Inositol
Lidocaine
Starches
Methapyrilene
Sucrose
Acetylprocaine
Dextrose
Scopolamine
Paracetamol
Phenobarbital
Methaqualone



FIGURE 1. Fundoscopic image of the retina.

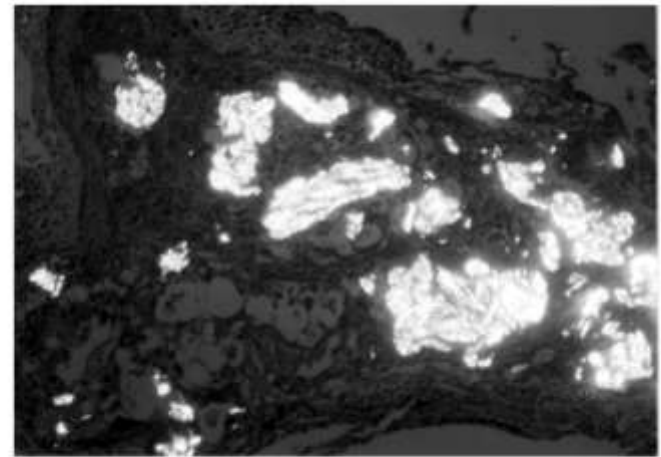
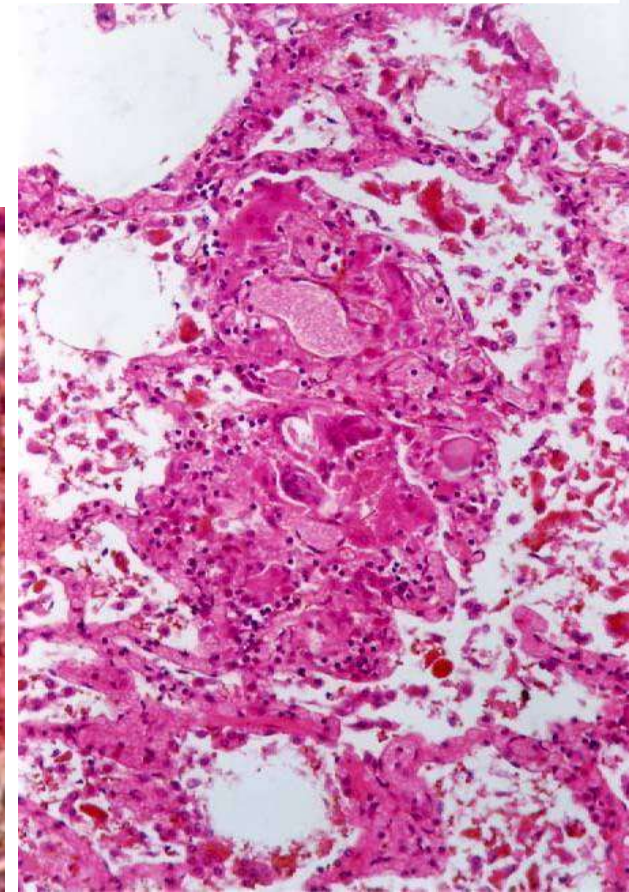
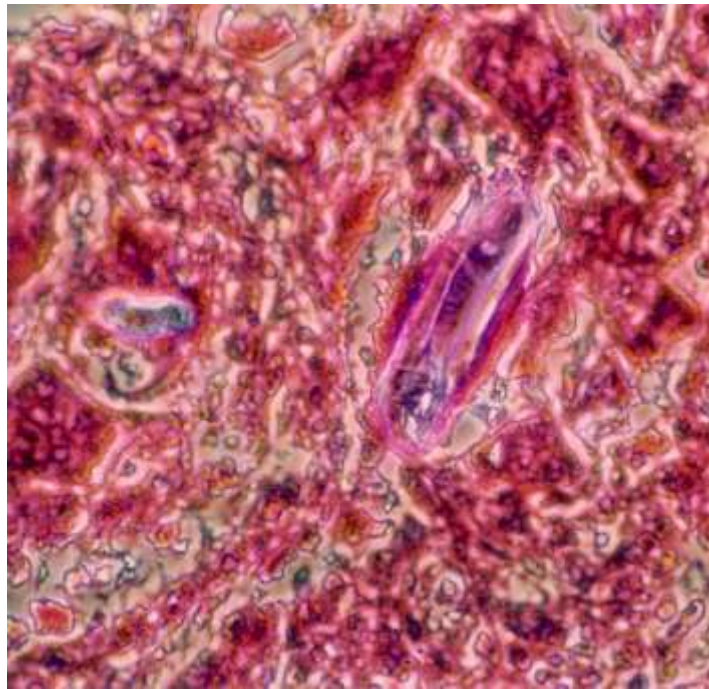
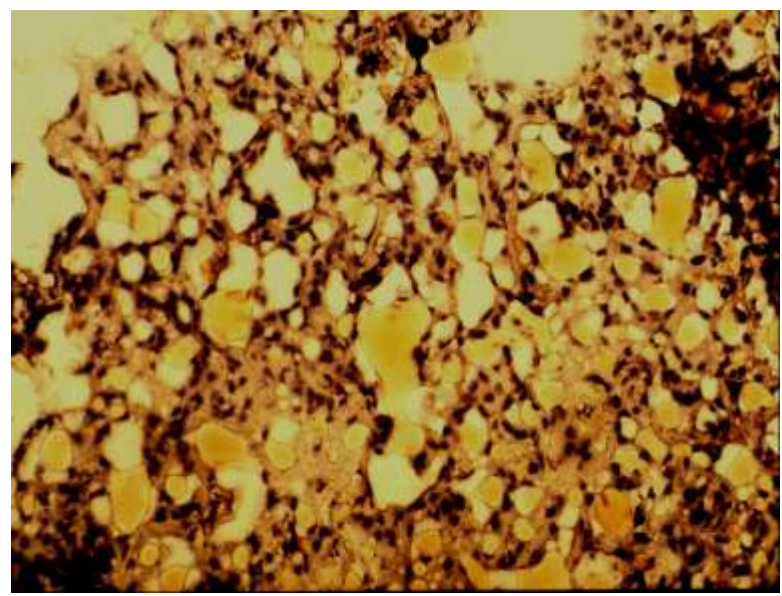
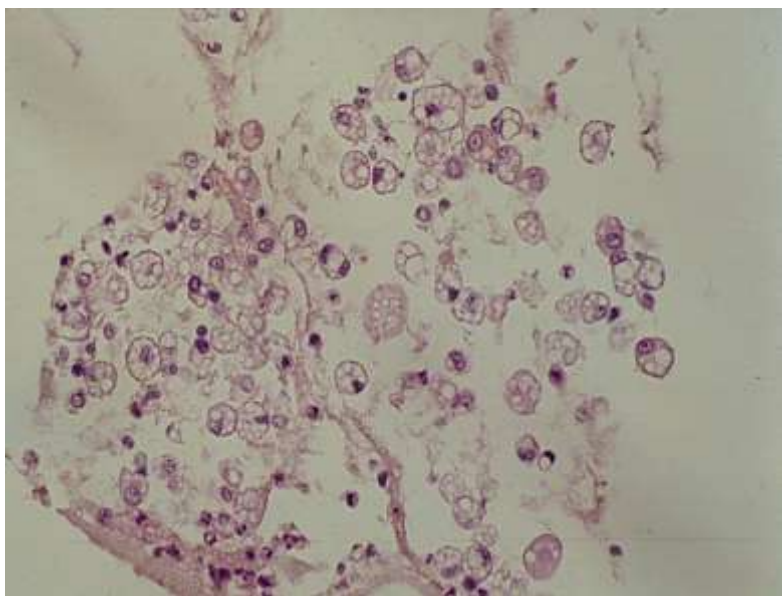


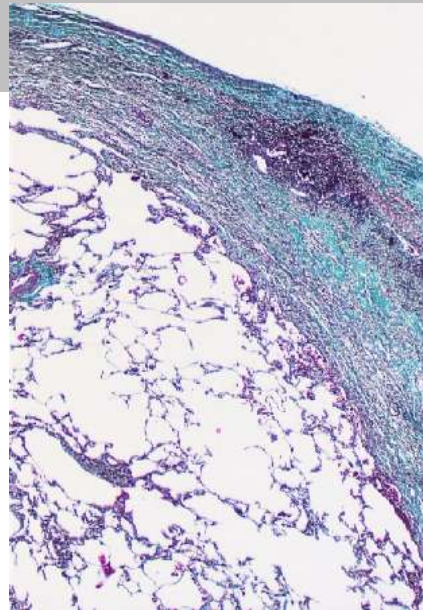
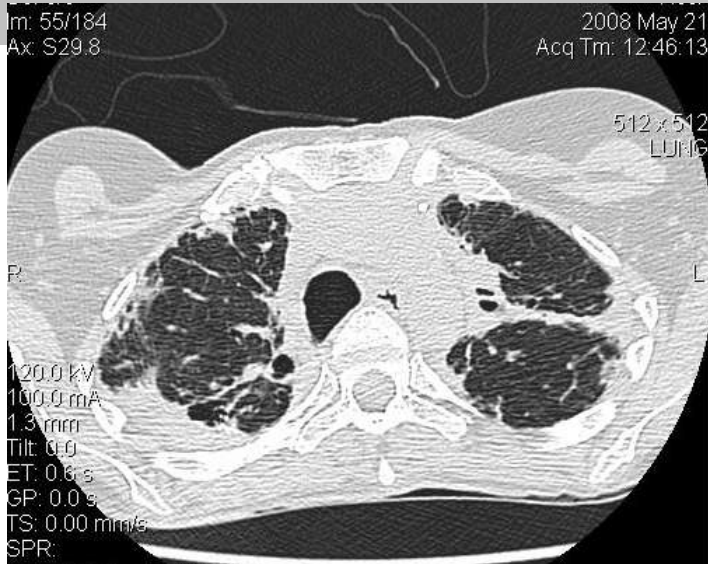
FIG. 3 The embolic material in the pulmonary arteries shows intense birefringence when examined under polarized light.  $\times 400$ .







# PPFE



- ▣ Dyspnea, chest pain
- ▣ Platythorax
- ▣ Restrictive lung function defect, often severe
- ▣ Distinctive imaging
- ▣ Significant Hx: Lung Tx 50%. Exposure to cyclophosphamide 10%

# Nonthrombotic pulmonary embolism

## ▣ Fluid silicone (Schmid 2005)

▣ Hypoxemia: 92%

▣ DAH: 64%

▣ Hemoptysis: 3

▣ Fatality rate

❖ 8/33

❖ 6/6 if neurological  
symptoms  
present

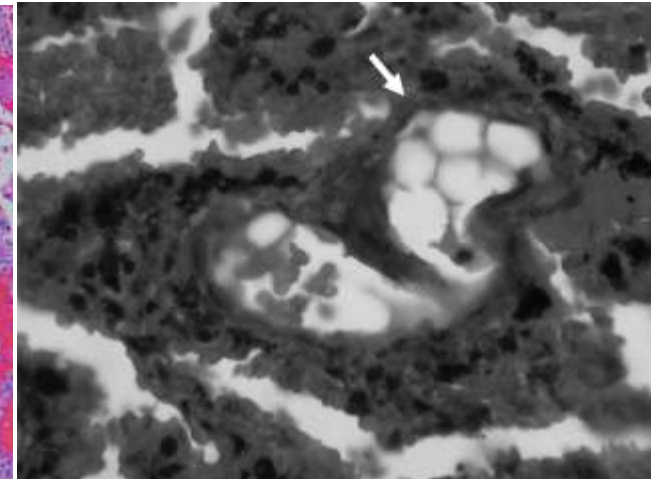
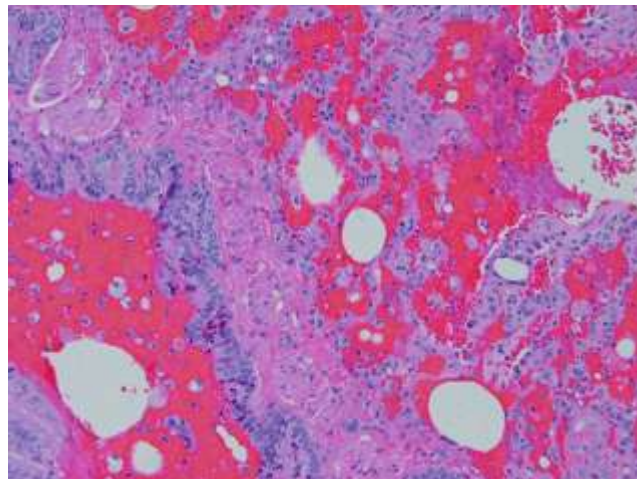
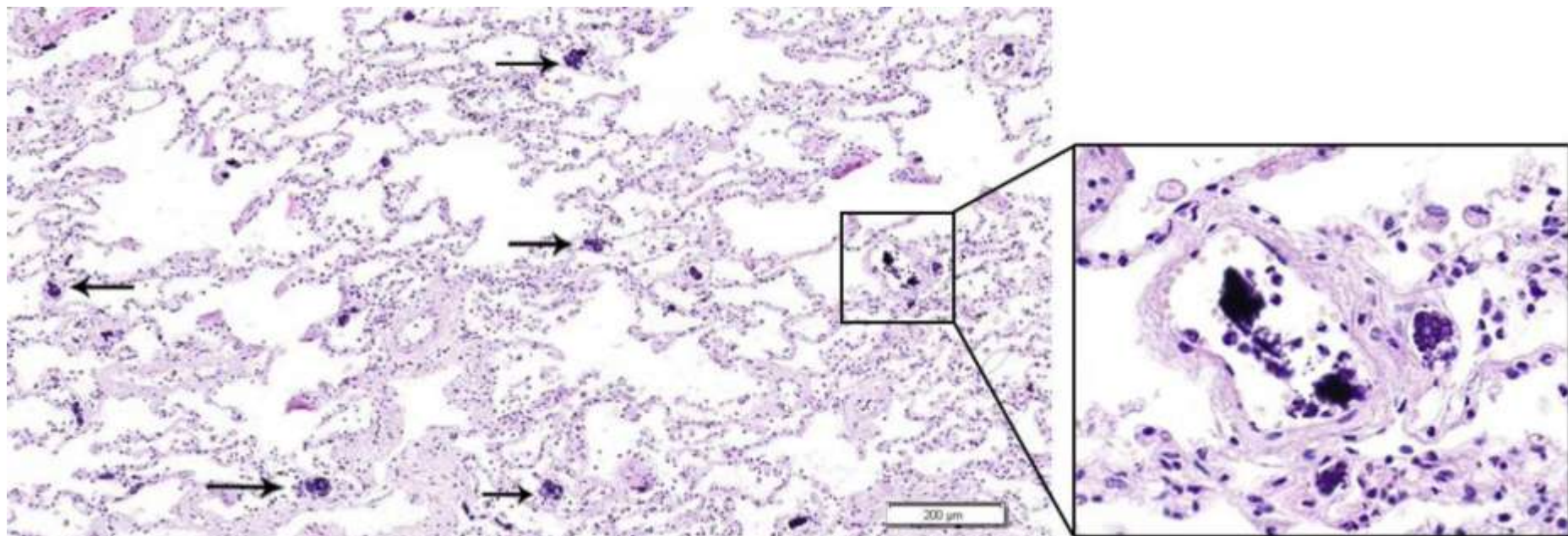




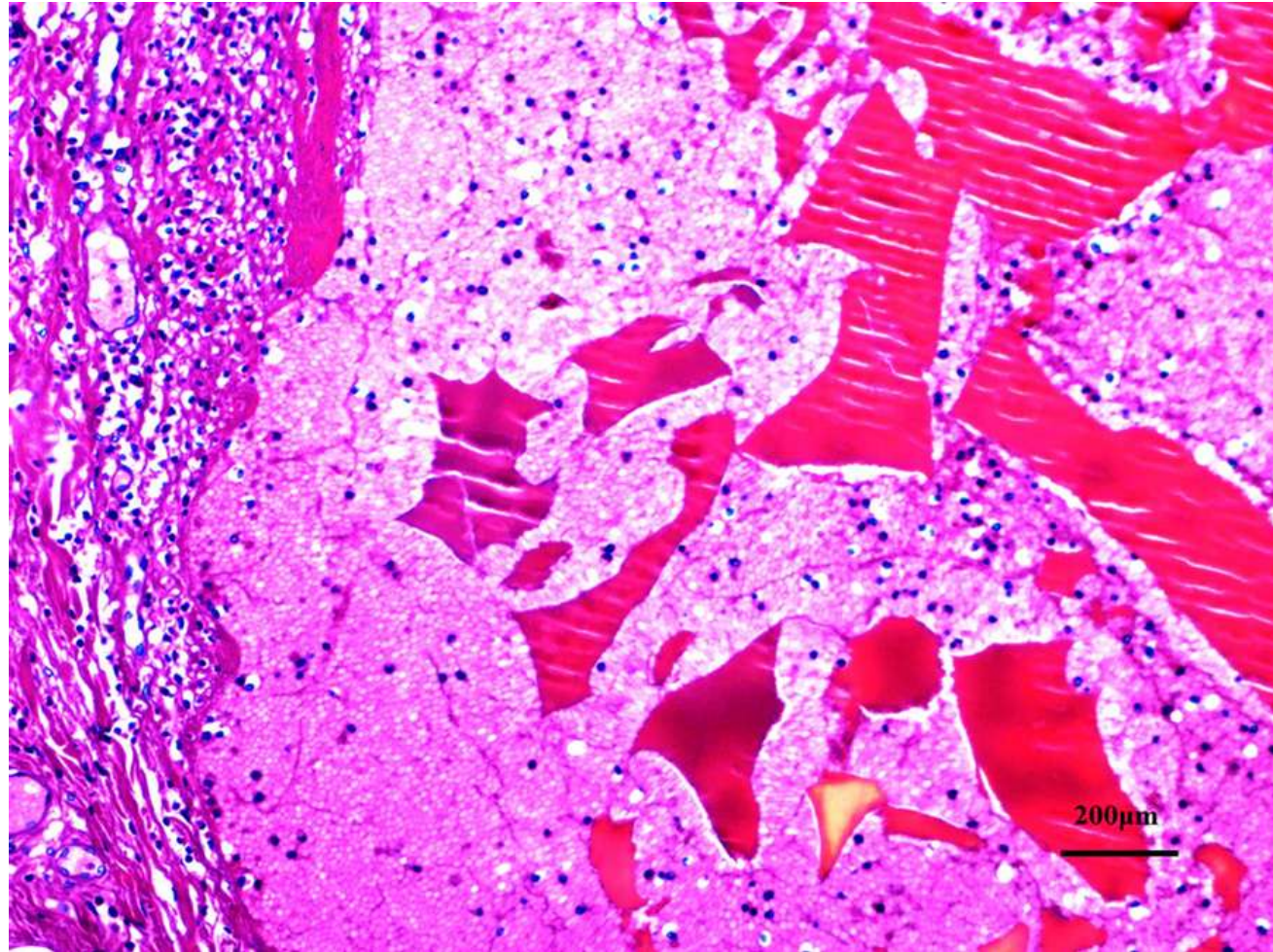


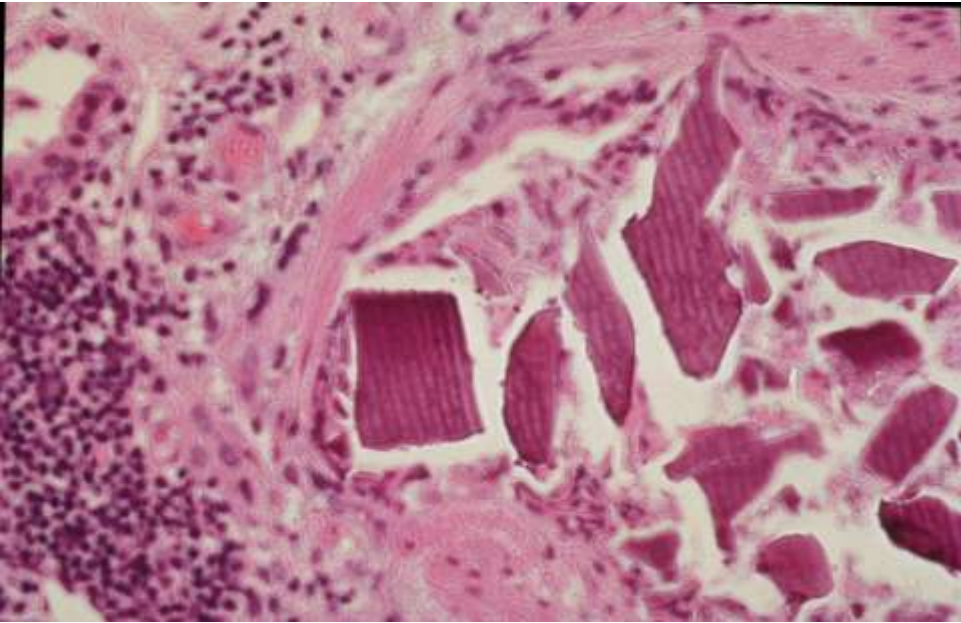
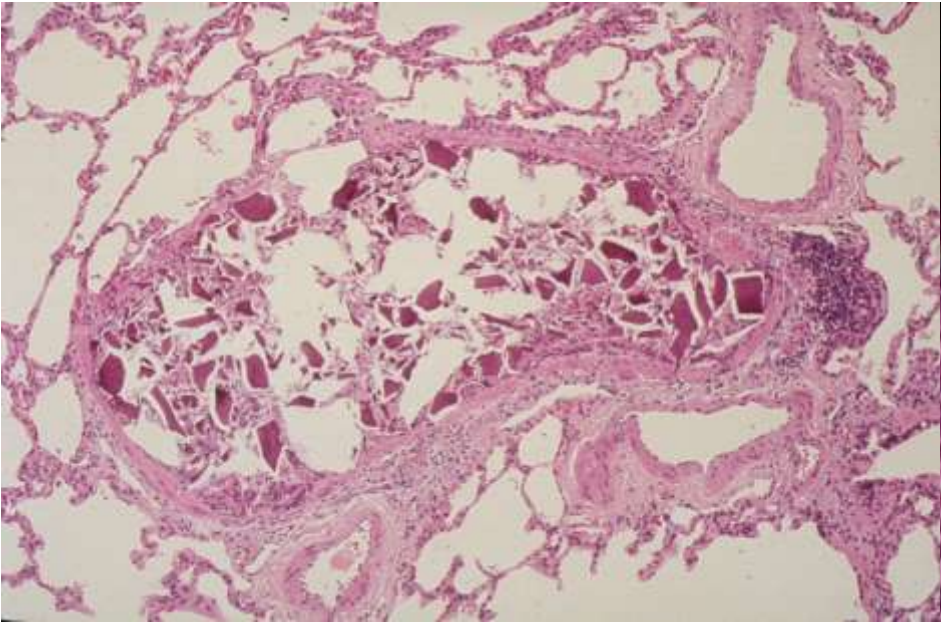
Fig. 1. Cement material in the pulmonary arteries.



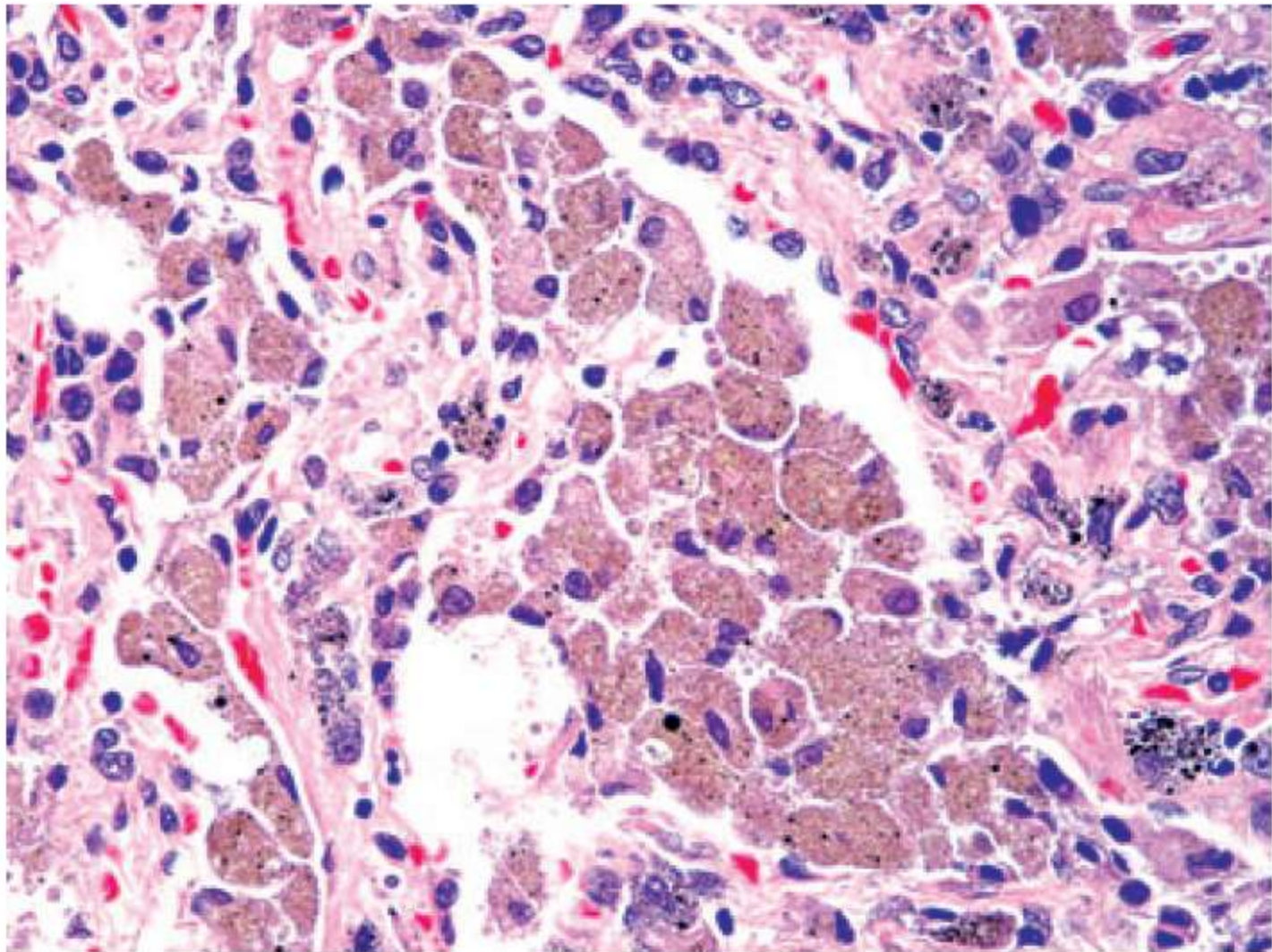


- Hydrogel
- Hyaluronate

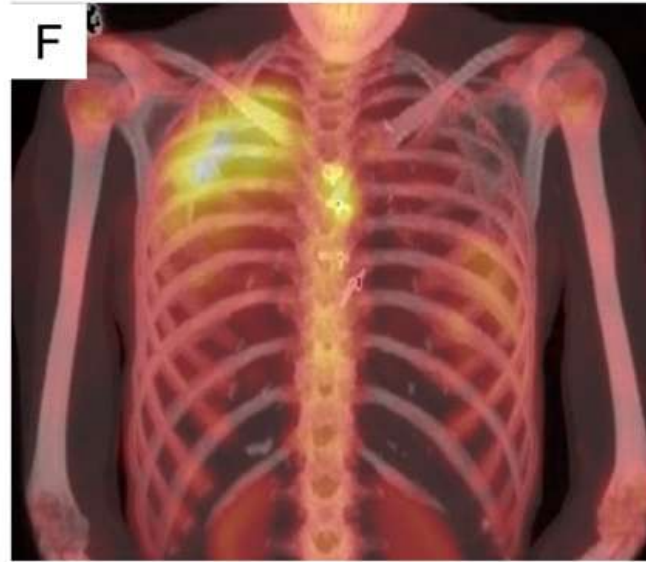
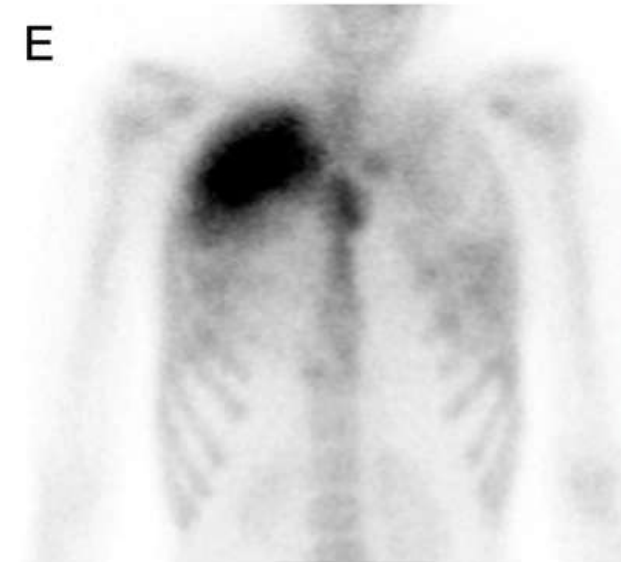
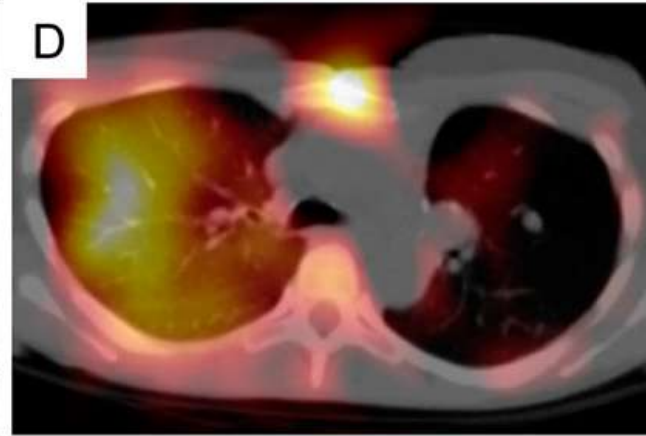
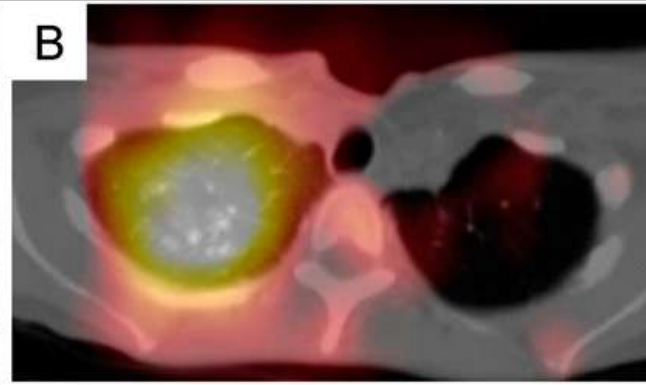
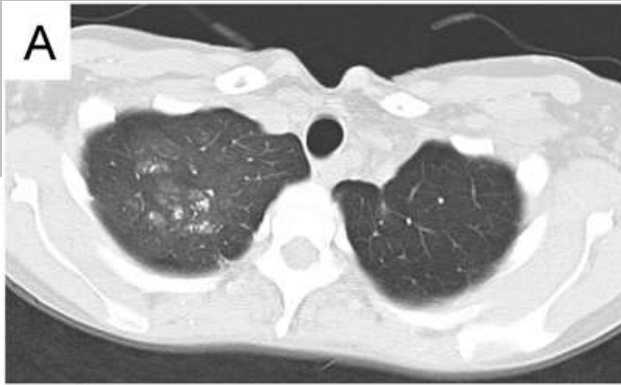








**Figure 11.** Intra-alveolar brown pigmented macrophages in a cannabis user.







## ❑ **Illicit drug manufacture/processing: Meth lab**

- ❖ Lineberry: Methamphetamine abuse: a perfect storm of complications  
Mayo Clin Proc 2006; 81: 77
- ❖ O'Neill *et al.* Methamphetamine laboratory-related burns in Western Australia - Why the explosion?  
Burns 2011



## ❑ **Carriage**

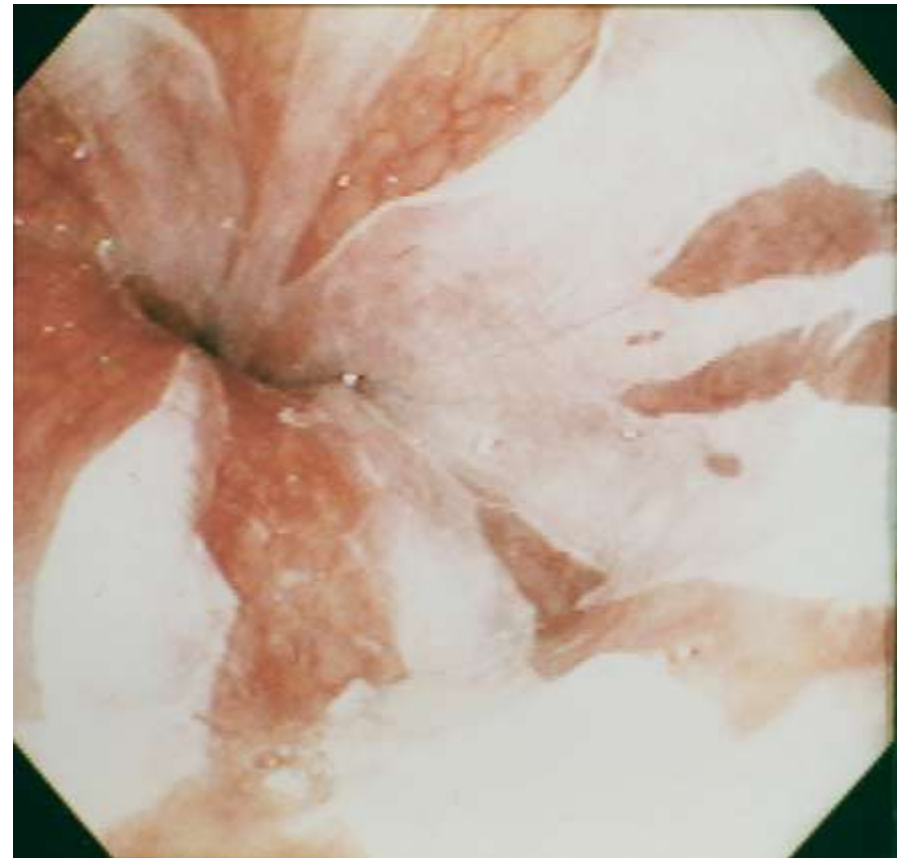
- ❑ **Body packers**
- ❑ **Ab Hamid. Characteristic imaging features of body packers: a pictorial essay**  
Jpn J Radiol 2012

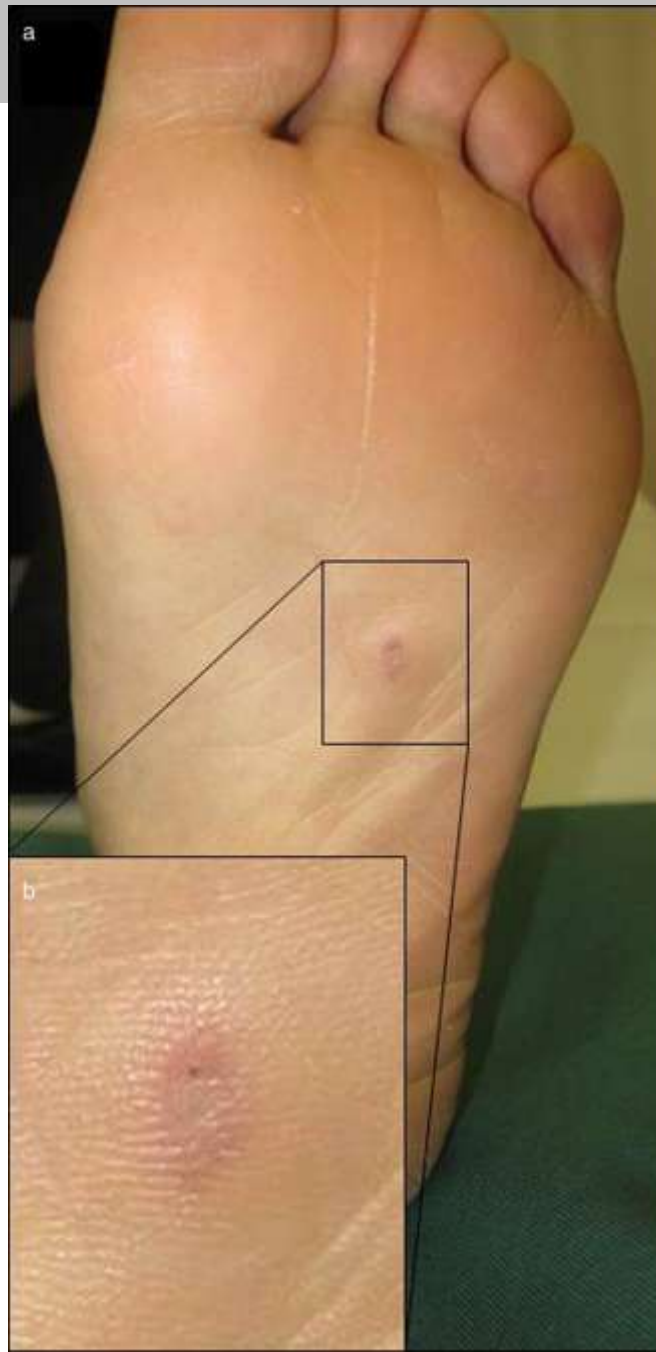




## ❑ Associated findings

- ❑ Pneumomediastinum
- ❑ Candy cane esophagus







## ■ Pill aspiration



# CHEST

## Special Features

### **“Pills” and the Air Passages**

*Elif Küpeli, MD; Danai Khemasuwan, MD, MBA; Pyng Lee, MD, FCCP;  
and Atul C. Mehta, MD, FCCP*

Aspiration of a medication in the airways in any form produces a variety of adverse effects, both local and systemic. Furthermore, specific reaction of the airways to each type of pill strongly affects the outcome. It is crucial for pulmonologists and emergency medicine specialists to acknowledge this clinical entity. In addition, airways have been increasingly used to deliver medications such as insulin and prostacycline. These aerosolized medications can also cause local as well as systemic side effects. We review the local and systemic reactions of these “pills” accessing the airways either by incidental aspiration or iatrogenic administration. We address clinical presentation, mechanism of injury, diagnosis, and management of complications of these pills in the air passages.

*CHEST 2013; 144(2):651–660*





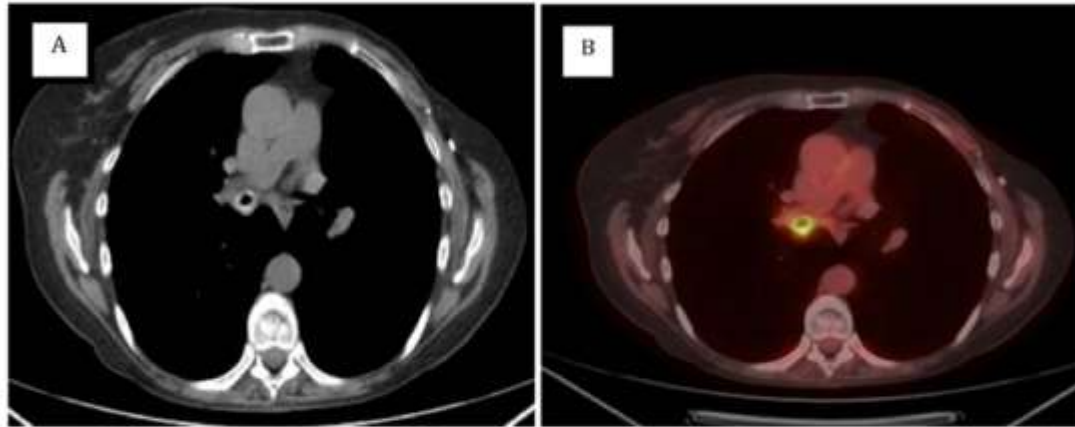
FIGURE 2. Rapid expansion of a sucralfate tablet is seen 30 s after placing it on a wet surface (*left*), compared with a dry tablet (*right*).



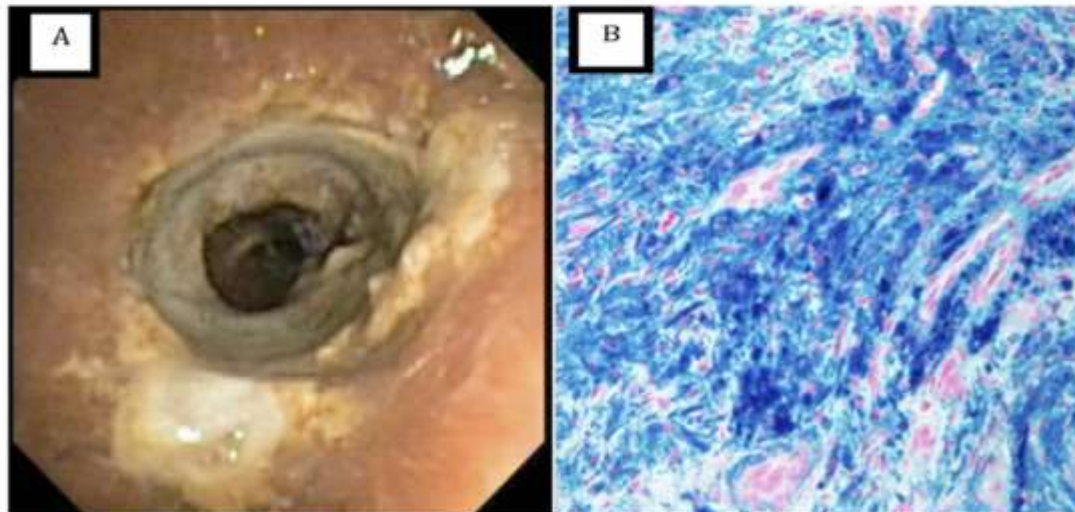
# The Iron Lady

Horiana B. Grosu<sup>1</sup>, Carlos A. Jimenez<sup>1</sup>, Georgie A. Eapen<sup>1</sup>, David Ost<sup>1</sup>, Cesar Moran<sup>1</sup>, and Rodolfo C. Morice<sup>1</sup>

<sup>1</sup>Department of Pulmonary Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas



**Figure 1.** (A) Computed tomography image with circumferential thickening of the bronchus intermedius. (B) Positron emission tomography-computed tomography image with circumferential fluorodeoxyglucose-avid area of the bronchus intermedius.



**Figure 2.** (A) Bronchoscopic view of bronchus intermedius with brown staining and necrosis of the mucosa. (B) Biopsy specimen showing strong positive reaction for iron.

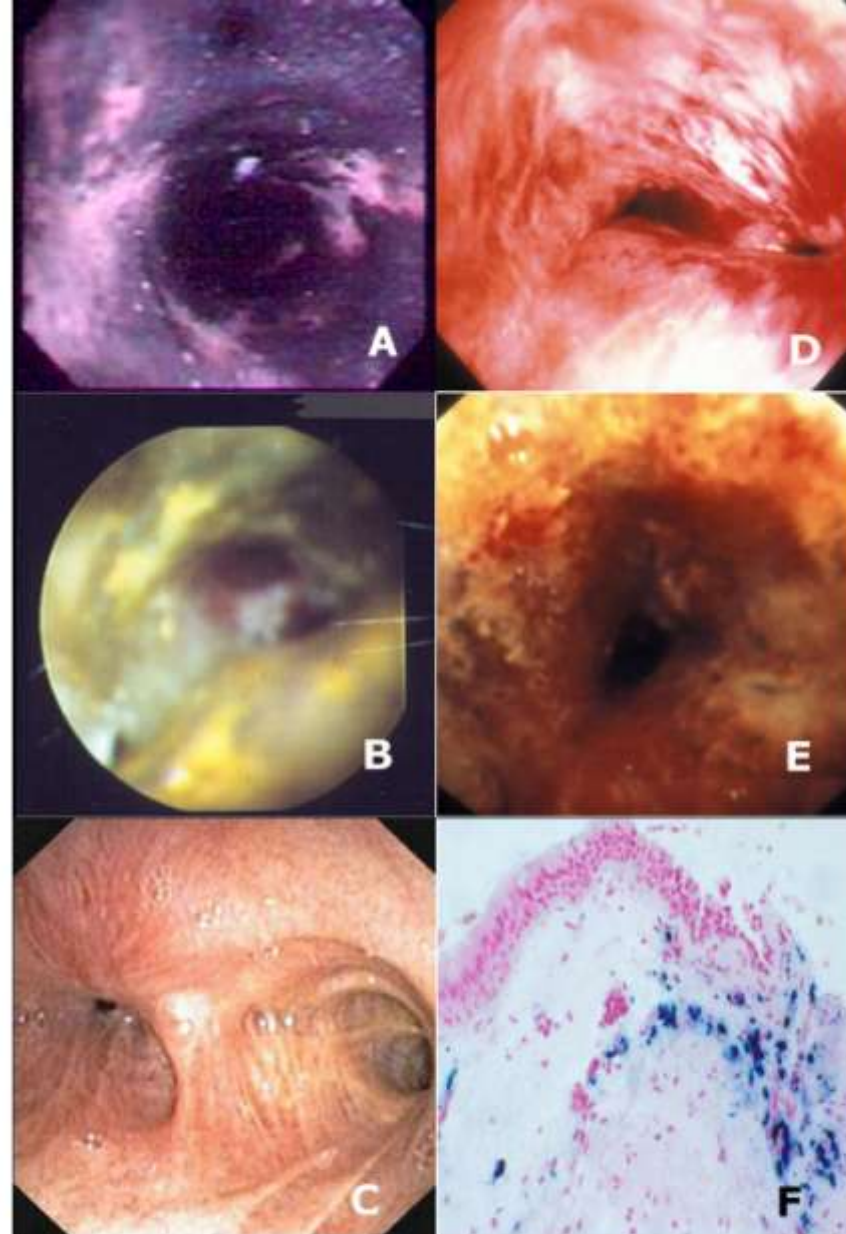


FIGURE 1. A, Charcoal in the tracheobronchial tree. (Reprinted with permission from Rajamani et al.<sup>6</sup>) B, Bronchus intermedius inflammation at day 1 after potassium-pill aspiration. Note, no foreign body was seen in the bronchus intermedius on day 1. C, Bronchus intermedius inflammation at 1 month after potassium-pill aspiration. (Reprinted with permission from Gudavalli et al.<sup>11</sup>) D, Intense inflammation of the bronchus intermedius following iron-pill aspiration. No foreign body was detected in the bronchus intermedius. E, Intense inflammation of right main stem bronchus following iron-pill aspiration. F, Endobronchial biopsy specimen revealing submucosal deposition of iron particles on Prussian blue stain (original magnification  $\times 200$ ).

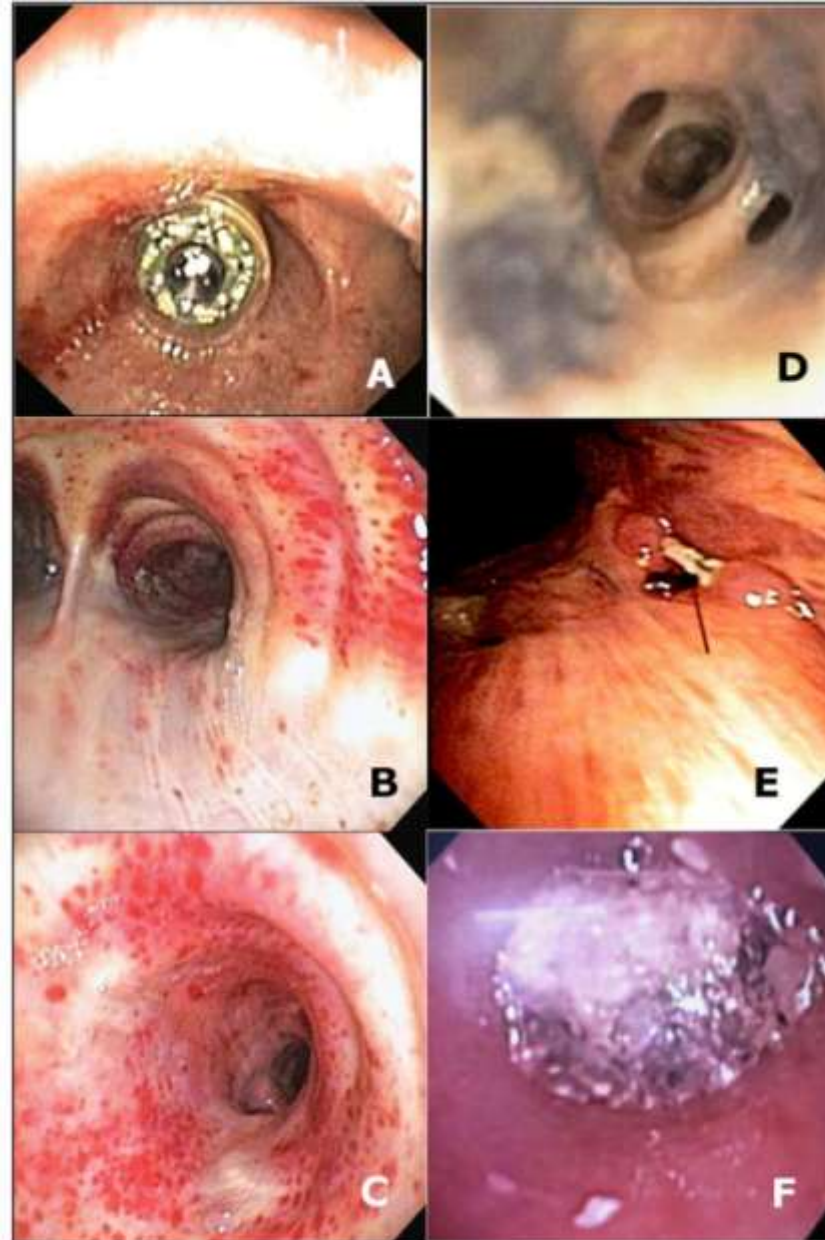
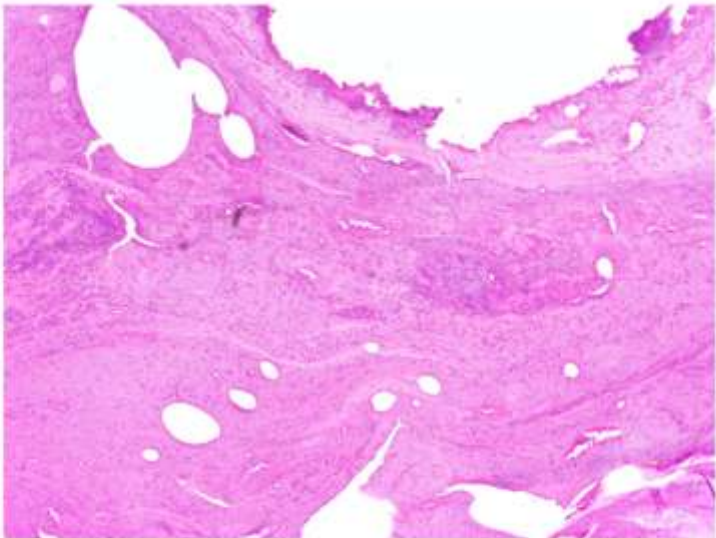


FIGURE 3. A, Aspiration of endoscopic capsule in the main bronchus. (Image courtesy of Thomas Gidea, MD, FCCP). B, Multiple submucosal petechiae involving trachea in a patient with hemoptysis who was taking clopidogrel. C, Multiple submucosal petechiae involving the left main bronchus in a patient with hemoptysis who was taking clopidogrel. (Reprinted with permission from Modrykamien et al.<sup>37</sup>) D, Black pigmentation involving the left lower lobe in a patient on amiodarone therapy. (Reprinted with permission from Lincoln et al.<sup>41</sup>) E, Late anastomotic dehiscence in a lung transplant recipient on serotinus (arrow). F, Near-total obstruction of the trachea from a cocaine-containing plastic bag. (Reprinted with permission from Narula et al.<sup>35</sup>)





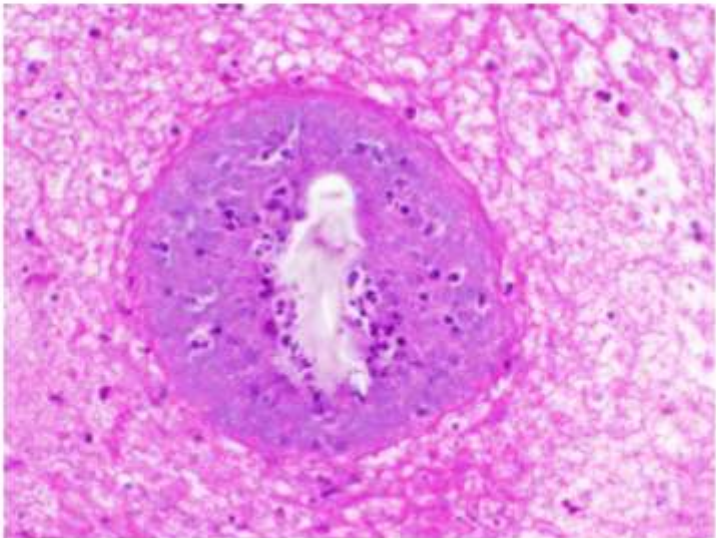
**Figure 1.** Trachea obstructed with large, wax-like plugs and pseudomembranes.



**Figure 3.** Ulceration of respiratory epithelium with intense inflammation.



**Figure 2.** Carina and right mainstem bronchus with wax-like plugs and pseudomembranes.



**Figure 4.** Multinucleated giant cell with crystalline foreign material.

# Exclusion of other causes

- **Infection**

- **Other drugs**

  - Concomittant meds

  - Remote exposures

  - Concealed exposure

- **Underlying disease**

- **Incidental disease**

# Improvement upon selective withdrawal

## □ Time to improvement

- ▣ Issues of antibiotics and Pneumocystis coverage
- ▣ Parallels time to onset
- ▣ Whenever:
  - ❖ severe pattern
  - ❖ unconvincing improvement
  - ❖ Infection ruled out
  - ❖ use corticosteroids liberally

## ■ Réchallenge rules

- As if you have to go to court
- Drug is vital
- There is no substitute
- Drug company formally contacted
- Committee for safety of medicines consulted
- Pneumotox formally consulted
- Patient informed
- Stepwise increase in dosage
- W/wo corticosteroids
- In the ICU

## ❑ **Preexisting ILD as a risk factor for DIRD?**

### ❑ **Yes**

- ❑ Amio
- ❑ Chemo
- ❑ TKI
- ❑ Methotrexate
- ❑ Anti-TNF

## ❑ **Usefulness of serial PFT?**



# Avoidable drug casualties

- ❑ **Compound on shelf or in soda bottles**
- ❑ **Pneumocystis prophylaxis failed**
- ❑ **Unprepared for anaphylaxis (chemo agents)**
- ❑ **Unnecessary blood transfusions**
- ❑ **Arrhythmia prophylaxis with amiodarone**
- ❑ **Amiodarone guidelines unimplemented**
- ❑ **Poor recognition: Angioedema, MetHb, TRALI, chest pain, nitrofurantoin, abused drugs, levamisole**

- ❑ **Salvage drugs (Methylene blue, adrenaline, icatibant) unavailable**
- ❑ **Intraoperative FIO<sub>2</sub> too high**
- ❑ **Mismanagement of anticoagulants incl. DOA**
- ❑ **I.V. where oral route would suffice**